whichever came first. Patients were excluded if they had type-1 diabetes or were prescribed rosiglitazone or troglitazone during the study period, or had stroke, MI, or brain injury prior to index date. Cox proportional hazards model was used to estimate risk for stroke or MI controlling for demographics, baseline comorbidities, medication use and resource utilization. **RESULTS:** A total of 85,253 patients with T2DM were included; total of 9053 (10.62%) patients were on PIO and 76,200 on Non-TZD cohort; a total of 178 (1.97%) patients who initiated PIO were hospitalized for stroke or MI compared to 1838 (2.41%) patients in the Non-TZD cohort ($P < 0.001$) during the follow-up period. The unadjusted incidence ratio for stroke or MI hospitalization associated with PIO relative to Non-TZD was 0.789 (95% CI: 0.677–0.921). After adjusting for baseline covariates in the multivariate analysis PIO patients were less likely to have stroke or MI hospitalization than Non-TZD patients, adjusted hazard ratio was 0.854 (95% CI: 0.732–0.997). **CONCLUSIONS:** T2DM patients initiated on pioglitazone were at reduced risk of having stroke or MI hospitalization than Non-TZD patients during the follow-up period. The result is consistent with clinical trial metaanalyses demonstrating lower risk of stroke or MI with pioglitazone compared to other oral antidiabetic agents.

PODIUM SESSION IV: MODELING METHODS – HANDLING UNCERTAINTY

MO9

HANDLING UNCERTAINTY IN THE CASE OF COMBINED END-POINTS

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Trials powered to show significant differences in a combined end-point invariably lack power when considering the individual end-points. Analyzing them individually leads to wide uncertainty margins which may have important consequences, especially when death is included. **OBJECTIVES:** To develop methods which recognize the process underlying the occurrence of endpoints and to analyze whether such methods lead to different point estimates and different results in probabilistic sensitivity analyses (PSA). **METHODS:** Two methods are compared with the "usual" approach, where individual events are modeled as the outcomes of a multinomial distribution. The first method heroically assumes that the risk reduction of the combined endpoints can be applied to the total event rate after which a partial multinomial model can be used for the events. The second method uses a Bayesian meta-regression which is programmed in Winbugs and includes data from earlier trials in the same area with and without the inclusion of explanatory variables. The two methods are illustrated using MI/stroke free survival as an endpoint from studies concerning lipid lowering therapy and studies concerning platelet inhibition. In the first, lipid levels are included as explanatory variables, in the second an unobserved common process is assumed. **RESULTS:** Analysis of data from six cholesterol trials and five platelet studies shows that assuming that the risk reduction applies to all events reduces the uncertainty by between 12–22% without affecting the point estimates. When using the Bayesian meta-regression models, the uncertainty is decreased by between 30%–80% with explanatory variables and between 16–45% without explanatory variables. However, point estimates may change more substantially as guided by the evidence from prior observations. **CONCLUSIONS:** Using Bayesian meta-regression to capture the dependence between endpoints in a combined endpoint-study may reduce the uncertainty of PSA results substantially. The magnitude of the reduction seems greater than when making heroic assumptions concerning the underlying dependence.

MO10

EARLY MODELLING: METHODS IN THE ECONOMIC ANALYSIS OF PRE-PHASE II PRODUCTS

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OBJECTIVES: Economic evaluations are increasingly used as tools to inform decision-makers about the cost-effectiveness of health technologies. Such evaluations are often undertaken during the late stages of the technology development (i.e. around the time of product launch or, in some cases, post-launch). However, there is an increasing need for the manufacturers of the technology to appraise the likely cost-effectiveness of the intervention *before* making decisions on price and indication, as well as to inform the development of clinical trials. **METHODS:** Due to the simplified nature of such 'early analyses', there is no availability of Phase III trial data, or evidence of subtle interactions between parameters. The purposes of such an analysis are to allow the user to determine the relative importance of different parameter inputs, in order to inform decisions on pricing, target populations and further research. This presentation outlines the key advantages and limitations of early modelling, and how the decision maker should interpret such analyses. **RESULTS:** This study demonstrates that early modelling is a vital exercise even (and, sometime, especially) when there is a significant lack of cost and effectiveness data. Early models can be an effective tool for determining price and target indications. A variety of outputs are demonstrated that will maximise the usefulness of such models to the decision maker. **CONCLUSIONS:** Even when there is a lack of Phase III data, economic models are a useful tool. However, the approach to modelling in such circumstances is significantly different to that when 'full' models are prepared. This study demonstrates how the value of early models can be increased, using a number of key outputs.

MO11

WHEN DOES VALUE OF INFORMATION ANALYSIS ADD VALUE?

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Value of information (VOI) is a monetary measure of the impact of uncertainty on a decision, quantified in terms of the expected value of perfect information. When uncertainty in control parameters is high, new information will carry high value in improving the value of a decision. Conversely, if parameters are known precisely, new information would not be considered valuable. VOI analysis is intuitively appealing, aims to improve our interpretation of the findings of health economic evaluations, and help plan further work—indeed, it is being declared mandatory in some jurisdictions. The implications of inaccurate or incomplete VOI analyses is potentially great, however; overestimating VOI leads to wasted funds on unnecessary research and delays in getting new treatments to markets, while underestimation exaggerates the strength of a possibly false decision. In this research, we provide a conceptual overview of VOI and discuss some of the key challenges involved in its proper use, with particular focus on the elements that are not being discussed: components that may bear the largest uncertainty such as the structure of the underlying model, the choice of modeling technique and the way in which the core control parameters are formulated and estimated.

MO12

COMPARISON OF THREE META-MODELS FOR UNCERTAINTY ANALYSIS

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Meta-models could reduce simulation time when running probabilistic sensitivity analyses (PSA) in complex cost-effectiveness analyses models. **OBJECTIVES:** To compare approximations of PSA outcomes by Ordinary Least Squares (OLS), Spatial Interpolation (SI) and Gaussian Process (GP) in terms of accuracy and computation time using a simple example. **METHODS:** Three meta-models are used to fit the relationship between inputs and outputs considering a cost-effectiveness model addressing cardiovascular treatment and using a selection of well chosen combinations of inputs. Using separate models for both incremental costs and incremental effects, and varying the number of design-points, accuracy is measured by comparing the Root Mean Squared Error (RMSE), as comparing thousand out-of-sample predictions of the meta-models with the corresponding outputs of the cost-effectiveness model. Computation time was defined as programming and running time. The Gaussian Process emulator is used in combination with regression. **RESULTS:** The PSA results of the cost-effectiveness model were not linear (RESET test) in both costs and effects but the linear model showed relatively high R-squares (0.7 and 0.85). Based on RMSE, the GP gives the best results, followed closely by SI. OLS has the smallest computation time, followed by GP and SI. Latter difference mostly explained by difference in programming time. The fewer design points for the meta-models, the smaller the gap between OLS and the interpolation-based models. **CONCLUSIONS:** GP/SI had best accuracy but needed most computation time, while OLS is quickest but the least accurate. The difference in accuracy between SI and GP is explained by the non-linearity of the relationship. The superiority of GP over SI decreases with increasing numbers of design points.

PODIUM SESSION IV: PRO/QOL METHODS – DEVELOPMENT

PR5

TRANSLATION AND LINGUISTIC VALIDATION: EVIDENCE TO SUGGEST THAT AN IN-COUNTRY REVIEW IS NECESSARY

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OBJECTIVES: The use of in-country reviews in the translation process of PRO measures is an important process. It allows for an existing language version to be modified for use in another country where the same language is spoken. The following languages are examples of where this can apply: English, Portuguese, Spanish, Chinese, Arabic, Russian and French. If a translation completed for one country is not reviewed for use in another, there is a risk that the translation may not be linguistically or culturally valid in the new country. This study sets out to outline the level of changes made when carrying out this process. **METHODS:** A sample of in-country reviews was taken from the translation of the POLO Chart measure. A total of 9 languages were reviewed. All changes that were made to any of the translations as a result of the in-country review were assessed according to whether the change was made as a result of a definitive linguistic and/or cultural difference (in the opinion of the in-country reviewer) or whether the change was made based on subjective preferences on behalf of the reviewer. **RESULTS:** A total of 213 changes were made across the 9 languages. The majority (140) of changes made were considered to be essential changes which were as a result of linguistic and/or cultural differences between the countries. More changes were made to the Chinese, Portuguese, and Spanish translations than to the English. **CONCLUSIONS:** In-country reviews are very useful in the translation process of PRO measures. A large number of changes made across the 9 languages and the fact that the majority of changes made to the translations are considered to be essential based on linguistic and/or cultural differences suggest that the in-country review is an important process to undertake.